AF/1623 $

DOCKET NO.: ISIS-2710 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Krotz et al. **Confirmation No.: 1518**

Application No.: 09/032,972 **Group Art Unit: 1623**

Filing Date: February 26, 1998 **Examiner: Lawrence E. Crane**

For: METHODS FOR SYNTHESIS OF OLIGONUCLEOTIDES

DATE OF DEPOSIT: July 23, 2003

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID, ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

John A Harrelson, Jr.

TYPED NAME: John A. Harrelson, Jr.
REGISTRATION NO.: 42,637

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on **May 30, 2003**.

2. STATUS OF APPLICANT

☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27 .

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:

☐ an Independent Inventor

☐ a Small Business Concern

☐ a Nonprofit Organization.

3. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.

☐ Applicant petitions for an extension of time under 37 CFR § 1.136 (fees: 37 CFR § 1.17(a)-(d)) for the total number of months checked below:

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
☐ ONE MONTH EXTENSION OF TIME	$55	$	$110	$
☐ TWO MONTH EXTENSION OF TIME	$205	$	$410	$
☐ THREE MONTH EXTENSION OF TIME	$465	$	$930	$
☐ FOUR MONTH EXTENSION OF TIME	$725	$	$1450	$
☐ FIVE MONTH EXTENSION OF TIME	$985	$	$1970	$
☐ LESS ANY EXTENSION FEE ALREADY PAID	minus	($)	minus	($)
☒ APPEAL BRIEF	$160	$	$320	$320
TOTAL FEE DUE		$0		$320

4. FEE PAYMENT

☒ A check in the amount of **$320.00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

☐ Please charge Deposit Account No. 23-3050 in the amount of **$ .00**. This sheet is attached in duplicate.

5. FEE DEFICIENCY

☒ If any additional extension and/or fee is required, this is a request therefor and to charge Deposit Account No. 23-3050.

☒ If any additional fee for claims is required, charge Deposit Account No. 23-3050.

6. ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: July 23, 2003

John A. Harrelson, Jr.
Registration No. 42,637

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

ISIS-2710 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Achim H. Krotz et al. **Confirmation No.: 1518**

Serial No.: 09/032,972 **Group Art Unit: 1623**

Filed: February 26, 1998 **Examiner: L. E. Crane**

For: Methods for Synthesis of Oligonucleotides

I, John A. Harrelson, Jr., Registration No. 42,637 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

On: **July 23, 2003**

John A. Harrelson, Jr., Reg. No. 42,637

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 1.192

Applicants appeal the Final Rejection of Claims 1-42 in the Office Action dated February 4, 2003.

I. Real Party in Interest

Based on information supplied by Applicants and to the best of the undersigned's knowledge, the real party in interest in the above-identified patent application is ISIS Pharmaceuticals, Inc., which is the assignee of Achim H. Krotz and Vasulinga T. Ravikumar.

II. Related Appeals and Interferences

There are no other appeals or interferences known to Appellants, Appellants' legal representative, or the assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

III. Status of Claims

Claims 1-42 are pending in this patent application and are the subject of this Appeal. These claims appear in Appendix A.

IV. Status of Amendments

No amendments to the claims have been made since the issuance of the Final Rejection.

V. Summary of the Invention

The invention concerns methods for synthesis of linear oligonucleotides and other phosphorus-linked oligomers that utilize *inter alia* a novel deprotection scheme that offers advantages over conventional synthetic schemes (page 6, line 30 to page 7, line 34). One key

advantage is the avoidance of dichloromethane and dichloroethane solvents in the deprotection scheme (*Id.*) The use of such solvents pose a barrier to relatively large scale synthesis of oligonucleotides because of disposal and efficiency issues (page 6, lines 18-28). The methods of the invention comprise the steps of attaching a 5'-O-protected nucleoside to a solid support; deprotecting the 5'-hydroxyl of the nucleoside with a protic acid in a solvent that consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent; reacting the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound to produce a covalent linkage therebetween; and then oxidizing or sulfurizing the covalent linkage (page 6, line 32 to page 7, line 13). The post solid support coupling steps are repeated at least once for subsequent couplings of additional activated phosphorus compounds (page 7, lines 14-17). At the conclusion of the synthesis, the oligomer is cleaved from the solid support (page 7, line 18).

VI. Issues On Appeal

This appeal seeks to resolve two issues:

1. Whether the Examiner has demonstrated that the subject matter of claims 1-42 would have been obvious to those of ordinary skill in the art over U.S. Patent No. 5,705,621 ("Ravikumar", assigned to the owner of the instant patent application) in view of U.S. Patent No. 4,973,679 ("Caruthers") and further in view of U.S. Patent No. 5,548,076 ("Froehler") and further in view of Sproat et al. (PTO-892 Ref. W), Conway, et al. (PTO-892 Ref. Y), Atkinson et al. (PTO-892 Ref. Z), and Sproat et al. (PTO-892 Ref. RA); and

2. Whether the Examiner has demonstrated that the subject matter of claims 1 -42 would have been obvious to those of ordinary skill in the art over Horn et al., *Nucleic Acids Research* **1989**, *17*, 6959-6967 ("Horn WA"), in view of Horn et al., *Nucleosides and Nucleotides*, **25**, 4842-4849 (1997) ("Horn UA").

VII. Grouping of the Claims

For the first ground of the rejection, Applicants believe that all claims stand or fall together. For the second ground of the rejection, Applicants believe that claims 1-5, 7, 8, 11-26, and 28-42 stand or fall together but that claims 6, 9, 10 and 27 should be considered separately.

VIII. Argument

First Issue-- There is no basis for the rejection of Applicant's claims for obviousness over the recited multiple combination of references.

The Examiner's rejection of claims 1-42 is improper because there is no evidence of record indicating that persons of ordinary skill would have been motivated to combine the teachings of the multiple cited references. Such persons would not have been motivated to combine the references' teachings in the manner the Examiner proposes. Given this lack of evidentiary support, the rejection for alleged obviousness should be withdrawn.

Claims cannot be found obvious in view of a combination of references unless the prior art itself suggests the desirability of the combination. *Berghauser v. Dann*, 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir.

1984). There must be something in the prior art that would have motivated persons of ordinary skill to make the combination. *In re Stencel*, 4 U.S.P.Q.2d 1071, 1073 (Fed. Cir. 1987), accord, *Ex parte Marinaccio*, 10 U.S.P.Q.2d 1716 (Pat. Off. Bd. App. 1989) (combining references is improper absent some teaching, suggestion, or motivation for the combination in the prior art).

Obviousness cannot be established by merely showing that it would have been **possible** for a person of ordinary skill to combine certain references. There must be **affirmative evidence** that such a person would have been "impelled" to make the combination. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993) (citations omitted, emphasis added).

The Examiner admits that at least two parts of the instant claims are not disclosed by Ravikumar or the other six cited references (page 2 of the February 4, 2003 Final Rejection). The Final Rejection quite correctly states that the art does not show "i) the choice of solvent or solvent mixture present for deprotection strep (c) and ii) the choice of substrate as a linear oligonucleotide as opposed to the branched oligonucleotide of the prior art" (*Id.*). In an attempt to fill the gaps in the art, the Examiner alleges that Caruthers and Froehler "motivate the selection of practically any organic solvent or solvent mixtures which will dissolve the reactants and not otherwise interfere with the intended synthetic transformation." However, this is not a correct characterization of the cited references. The Final Rejection cites four solvents– each outside the scope of the instant claims-- disclosed in the Caruthers reference as a basis for the alleged motivation. These solvents, as admitted by the Examiner (page 4 of the February 4, 2003 Final Rejection), were in the context of the coupling step **not the deprotection step**. The Office Action, however, alleges that "the same

teaching *appears* to also apply to the deprotection step" (*Id.*, emphasis added). Applicants see no basis for this statement as the Caruthers reference explicitly states that only the solvent teaching is in the context of the coupling reaction (column 5, lines 10-14 of the Caruthers reference).

The Froehler reference also does not motivate the selection of the solvents used in the instant invention for the deprotection step. Froehler, which does not disclose the instant deprotection solvents, merely states that other deprotection procedures are known to one skilled in the art. It clearly does not follow that the instantly used solvents would selected by one skilled in the art. Applicants respectfully submit that nothing in the remaining cited art shows or motivates Applicant's use of the solvent of the instant claims. The Examiner alleges that disclosures in the Sproat, Conway, and Atkinson references show that certain phosphoramidite compounds are soluble in toluene and benzene (page 6- 7 of the Final Rejection). The Examiner then argues that the solubility is motivation for the selection of the instant deportection solvents. Applicants submit that solubility is but one of many factors used in the selection of a reaction solvent. At most, such evidence is obvious to try argument and lacks the legally required motivation for support of an obviousness rejection.

Without the legally required teaching of motivation to make the combination or modification, the rejection is improper. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1998). The cited art does not provide the teaching or motivation asserted by the Examiner. As such, the rejection should be withdrawn.

Second Issue-- There is no basis for the rejection of Applicant's claims over Horn et al., *Nucleic Acids Research* 1989, *17*, 6959-6967 ("Horn WA"), in view of Horn et al., *Nucleosides and Nucleotides*, 25, 4842-4849 (1997) ("Horn UA").

Claims 1-42 are rejected under 35 U.S.C.§103(a) for alleged obviousness over Horn et al., *Nucleic Acids Research* **1989**, *17*, 6959-6967 ("Horn WA"), in view of Horn et al., *Nucleosides and Nucleotides*, **25**, 4842-4849 (1997) ("Horn UA"). There is no evidence of record indicating that persons of ordinary skill would have been motivated to combine the teachings of the cited references, or that such persons would have been motivated to combine the references' teachings in the manner the Examiner proposes. In fact, the available evidence indicates that those of ordinary skill in the art would not have been motivated to make the combination or that such a combination would produce the invention of any instant claim. Given this lack of evidentiary support, the rejection for alleged obviousness is improper and should be withdrawn.

Even if one combined selected teaching of the cited art, one would not arrive at any claimed invention. The cited art, for example, does not disclose the use of the deprotection solvent of the instant claims with linear oligomers. The Examiner alleges that the Horn UA reference shows such a use. Horn UA, however, discloses use of toluene/CH_2Cl_2 deprotection solvent, not the solvent of the instant claims. The claim language "the solvent consists essentially of an aromatic solvent, an alkyl aromatic solvent, a halogenated aromatic solvent, a halogenated alkyl aromatic solvent, or an aromatic ether solvent"of instant claims 1 and 21 preclude use of CH_2Cl_2 solvent. Because the cited art cannot produce any claimed invention, the rejection is improper and should be withdrawn.

Further, Applicants assert that one skilled in the art would not look to the branched oligonucleotide art for deprotection schemes for linear oligonucleotides. The Horn WA reference

describes the synthesis of branched oligodeoxyribonucleotides. This reference states that the standard deprotecting reagent was found to be ineffective for deprotection of the synthesized branched DNA, and that trityl deprotection of such branched structures was achieved using 3% dichloroacetic acid in toluene. Applicants note that in the context of the present invention, i.e., synthesis of linear oligonucleotides, the occurrence of branched structures such as described in the Horn WA reference are contaminants to be avoided, and, in the event that such branch structures are produced, it is highly desirable to avoid deprotecting them, both to eliminate participation in further synthesis cycles, and in order to utilize the trityl groups to eliminate the contaminant from the final purified linear oligonucleotide. Further, the Horn WA reference states at page 6965:

> In our early attempts to synthesize **branched DNA**, we found it difficult to deprotect the multiple intramolecular dimethoxytrityl functions with **standard DCA/CH_2Cl_2** even with extended exposure (2). Under the assumption that dimethoxytrityl stacking stabilize the protection, we employed 3% (v/v) DCA in toluene. With this solution it was possible to rapidly and efficiently detritylate the branched materials (Figure 2). (emphasis added)

Thus, the Horn WA reference teaches 1) that **deprotection with dichloroacetic acid in methylene chloride is *standard***; and that 2) the toluene solution was needed for deprotection of **branched DNA**, which posed particular problems. As such, Applicants assert that those of skill in the art would not be led to use the stringent deprotection regime disclosed in the Horn WA reference for standard synthesis of linear oligonucleotides.

The Examiner has not set forth how any reference would have instructed the person of ordinary skill in the art to modify the reference teachings to afford the claimed invention. No

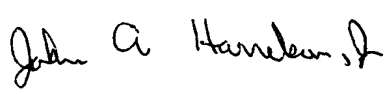
reference teaches or fairly suggests deprotecting the 5'-hydroxyl group of a linear oligonucleotide, with a protic acid, in a solvent system consisting essentially of an aromatic, alkyl aromatic, halogenated aromatic, halogenated alkyl aromatic, or aromatic ether solvent. Nor does any reference teach or fairly suggest to the person of ordinary skill in the art how to choose suitable deprotecting solvents from the myriad of possibilities. Absent these motivating factors, the Office Action has failed to establish that the person having ordinary skill in the art would have been motivated to substitute the instant solvent for the solvent of the prior art. As such, the rejection should be withdrawn.

Further, as applied to claims 6, 9, 10, and 27, the instant claims do not comprise any deprotection solvent discussed in the cited art. These instant claims do not use toluene or toluene/CH_2Cl_2 deprotection solvent. As discussed above, Horn UA requires the use of toluene/CH_2Cl_2 deprotection solvent. Thus, even if one were motivated to combine the cited art, one would not arrive at the invention of any instant claim. For at least this reason, Applicants request the rejection be withdrawn and the claims allowed.

IX. Conclusion

For the foregoing reasons, Applicants submit that claims 1-42 fully comply with the requirements of 35 U.S.C. § 103 (a). Applicants ask that this patent application be remanded with an instruction to both withdraw the outstanding rejections and allow the appealed claims.

Respectfully submitted,



John W. Caldwell
Registration No. 28,937

John A. Harrelson, Jr.
Registration No. 42,637

Date: **July 23, 2003**

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100